Kunutsor, S. K., Laukkanen, T., & Laukkanen, J. A. (2018). Cardiorespiratory fitness is associated with reduced risk of future psychosis: A long-term prospective cohort study. *Schizophrenia Research*, *192*, 473-474. https://doi.org/10.1016/j.schres.2017.04.042

Letter to the Editor

Cardiorespiratory fitness is associated with reduced risk of future psychosis: a long-term prospective cohort study

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Psychosis is a severe disabling condition and associated with increased morbidity as well as premature mortality.(McGrath et al., 2008) Though little is known about the etiology of psychosis, it is a partly preventable mental illness and life-style factors have been implicated in its development. Cardiorespiratory fitness (CRF), as measured by maximal oxygen uptake (VO_{2max}), is considered the gold standard for assessing aerobic capacity and is an index of cardiac and respiratory functioning.(Noonan and Dean, 2000) Cardiorespiratory fitness is well known to be strongly inversely and independently associated with the risk of cardiovascular disease (CVD)(Kodama et al., 2009) and all-cause mortality.(Kodama et al., 2009) Individuals with psychotic disorders have been shown to have lower CRF.(Vancampfort et al., 2015) Accumulating evidence suggests that people with psychotic disorders such as schizophrenia are at high cardiovascular risk and CVDs are the major contributing factors for the increased mortality rates in these individuals.(Olfson et al., 2015) Given that CRF is a major modifiable risk factor for CVD in the general population, we hypothesized that CRF could be related to the development of psychosis. In this context, we aimed to assess the association of CRF with future risk of psychosis, using a population-based cohort of 2,212 Caucasian men, who were apparently free from any mental illness during baseline assessments.

The current analysis employed the Finnish Kuopio Ischemic Heart Disease (KIHD) risk factor study which comprised a representative sample of middle-aged men aged 42-61 years recruited from eastern Finland. Details of recruitment methods, ethical permissions, and assessment of risk markers have been described in a previous report.(Kunutsor et al., 2017) Maximal oxygen uptake was used as a measure of CRF, which was assessed using respiratory gas exchange analyzers during cycle ergometer exercise testing. Repeat measurements were performed several years apart in a random subset of participants. A detailed description of the measurement of VO_{2max} has been reported elsewhere.(Kunutsor et al., 2017) Data on hospitalizations due to psychotic disorders were ascertained by linkage to the National Hospital Discharge Register. The diagnoses of psychotic disorders were made by qualified psychiatrists and details have been previously described.(Kunutsor and Laukkanen, 2017) For the current analysis, men on

antipsychotic medication at study entry (n=54) were excluded. Hazard ratios (HRs) with 95% confidence intervals (CIs) for psychosis were calculated using Cox proportional hazard models. All statistical analyses were conducted using Stata version 14 (Stata Corp, College Station, Texas).

The mean [standard deviation (SD)] age and CRF of participants at baseline were 53 (5) years and 30.4 (8.0) ml/kg/min respectively. During a median (interquartile range) follow-up of 25.2 (18.2-27.1) years, 215 hospital diagnosed psychotic disorders were recorded (annual rate 4.43/1000 person-years at risk; 95% CI 3.87 to 5.06). Overall, the age-adjusted regression dilution ratio of CRF was 0.58 (95% CI: 0.52 to 0.63), which suggests that the association of CRF with risk of psychosis using one-off or baseline measurements of CRF could under-estimate the risk by [(1/0.58)-1]*100 = 72%. Cardiorespiratory fitness was approximately linearly and inversely associated with risk of psychosis after adjustment for established risk factors (age, smoking status, history of diabetes, prevalent history of coronary heart disease, years of education, total cholesterol, and alcohol consumption). The age-adjusted HR for psychosis per 1 SD increase in CRF was 0.79 (95% CI: 0.67 to 0.92), which persisted on further adjustment for established risk factors 0.80 (95% CI: 0.68 to 0.95). The HR remained consistent on additional adjustment for total energy intake, socioeconomic status, physical activity, and C-reactive protein 0.82 (95% CI: 0.69 to 0.98). Comparing the top quartile versus bottom quartile of CRF levels, the corresponding adjusted HRs were 0.55 (95% CI: 0.37 to 0.82), 0.59 (95% CI: 0.39 to 0.90), and 0.64 (95% CI: 0.42 to 0.98) respectively. The associations were stronger after correction for within-person variability in CRF levels (**Table**).

In this first prospective evaluation of the association between CRF and risk of psychosis, our results show an inverse independent and approximately dose-response relationship between CRF and future risk of psychosis in middle-aged Caucasian men who had no pre-existing mental illness at study entry. Chronic inflammatory processes as well as oxidative stress have been implicated in the pathogenesis of psychotic disorders. (Feigenson et al., 2014; Owe-Larsson et al., 2011) Cardiorespiratory fitness, which is influenced by both genetic and environmental factors, is an index of the level of physical activity. Since

physical activity exerts its protective effects on adverse vascular outcomes via anti-inflammatory and anti-oxidant processes; (Ford, 2002) it is reasonable to postulate that these same pathways may partly underlie the protective relationship observed between CRF and future psychosis risk. It is well established that physical activity has important health benefits and confers long-term protection on the cardiovascular system and mortality.(Erikssen et al., 1998) Physical activity has also been shown to improve mental health and reduce care needs in people with psychotic disorders.(Scheewe et al., 2013) Taken together, the overall findings suggest that promoting good CRF levels via regular physical activity may protect against the development of mental illness such as psychotic disorders. Further research is needed to replicate this relationship and if CRF can be used to improve risk stratification of individuals at high risk of psychotic disorders.

The strengths of the current analysis include the use of a large-scale population-based prospective cohort of men recruited from the general population who were free from mental illness at baseline, long-term and complete follow-up of all participants, adjustment for a comprehensive panel of confounders, and correction for within-person variability in CRF levels. Our analyses were limited by the following: (i) the inability to generalize the findings to both genders, because the initial study sample comprised only men; (ii) the possibility of residual confounding, being an observational study, and (iii) the outcome was based on all types of psychotic disorders.

In conclusion, CRF is associated with reduced risk of future psychosis in an approximately graded dose-response pattern in middle-aged Caucasian men. The prognostic value of CRF for future psychosis risk deserves further evaluation.

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Table. Association of cardiorespiratory fitness and risk of psychosis

CRF (ml/kg/min)	Events/ Total	Model 1		Model 2		Model 3	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Baseline CRF							
Per 1 SD increase	215 / 2,221	0.79 (0.67 to 0.92)	0.003	0.80 (0.68 to 0.95)	0.009	0.82 (0.69 to 0.98)	0.027
Q1 (6.36-25.25)	72 / 556	ref		ref		ref	
Q2 (25.27-30.15)	51 / 555	0.62 (0.43 to 0.88)	0.008	0.62 (0.43 to 0.89)	0.010	0.63 (0.44 to 0.92)	0.016
Q3 (30.15-35.28)	51 / 555	0.66 (0.46 to 0.96)	0.028	0.66 (0.45 to 0.96)	0.030	0.68 (0.47 to 1.01)	0.053
Q4 (35.28-65.40)	41 / 555	0.55 (0.37 to 0.82)	0.004	0.59 (0.39 to 0.90)	0.013	0.64 (0.42 to 0.98)	0.039
Usual CRF*							
Per 1 SD increase	215 / 2,221	0.66 (0.51 to 0.86)	0.003	0.68 (0.51 to 0.91)	0.009	0.72 (0.53 to 0.96)	0.027
Q1 (6.36-25.25)	72 / 556	ref		ref		ref	
Q2 (25.27-30.15)	51 / 555	0.43 (0.23 to 0.81)	0.008	0.43 (0.23 to 0.82)	0.010	0.46 (0.24 to 0.86)	0.016
Q3 (30.15-35.28)	51 / 555	0.49 (0.26 to 0.93)	0.028	0.49 (0.25 to 0.93)	0.030	0.52 (0.27 to 1.01)	0.053
Q4 (35.28-65.40)	41 / 555	0.36 (0.18 to 0.72)	0.004	0.41 (0.20 to 0.83)	0.013	0.46 (0.22 to 0.96)	0.039

CI, confidence interval; CRF, cardiorespiratory fitness; HR, hazard ratio; ref, reference; Q, quartile; SD, standard deviation;

*, indicates correction for within-person variability in values of CRF, that is, the extent to which an individual's CRF measurements vary around a long-term average value ("usual CRF values")

Model 1: Adjusted for age

Model 2: Model 1 plus smoking status, history of diabetes, prevalent coronary heart disease, years of education, total cholesterol, and alcohol consumption

Model 3: Model 2 plus total energy intake, socioeconomic status, physical activity, and C-reactive protein